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In re Application of:		§	
	JENNIFER WEST, ET AL.	§	Group Art Unit: **1644**
		§	
Serial No.:	**09/935,168**	§	
		§	Examiner: **Phuong N. Huynh**
Filed:	**August 21, 2001**	§	
		§	
Title:	**"TISSUE ENGINEERING SCAFFOLD PROMOTING MATRIX PROTEIN PRODUCTION"**	§	Atty. Docket No: **Rice 103**

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EXAMINER: PHUONG N. HUYNH

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APPELLANTS' REPLY BRIEF PURSUANT TO 37 C.F.R. 1.193(a)

Sir:

In response to the Answer from the Examiner mailed April 7, 2004, Appellants present the following Reply Brief Pursuant to 37 C.F.R. 1.193(a).

Appellants respectfully assert that grave doubts exist as to the propriety of the rejections asserted by the Examiner in this case, due to the Examiner's misinterpretation of the scope of

Appellants' claims, the Examiner's misapplication of the prior art, and Appellants' demonstration of unexpected results.

I. The combination of Dinbergs *et al.* and WO 94/23740 fails to obviate Appellants' claimed invention.

A. The Examiner's rejection of claim 1 under 35 U.S.C. 103 in view of the combination of Dinbergs *et al.* and WO 94/23740 is improper.

In the Appeal Brief faxed February 3, 2004, Appellants demonstrated that Claim 1 is novel and nonobvious over the cited combination of Dinbergs *et al.* and WO 94/23740. *See* APPEAL BRIEF, at 6-10. In the Examiner's Answer, the Examiner reasserted the rejection over the cited art, and set forth the reasoning underlying the rejection. Appellants respectfully traverse the rejection, and respectfully assert that the Examiner's Answer fails to rebut Appellants' contention that claim 1 is novel and nonobvious over the cited references, for at least the following reasons.

1. The Examiner Has Improperly Construed the Scope of Claim 1.

In numerous instances in her Answer, the Examiner has improperly construed the scope of Appellants' claims, including claim 1. In so doing, the Examiner has improperly omitted certain limitations that are present in the claim, and that are not disclosed by the cited combination of Dinbergs *et al.* and WO 94/23740.

a. Contrary to the Examiner's assertion, Appellants' claimed method recites the enhancement of extracellular matrix production without increasing cellular proliferation.

The Examiner appears to perceive Appellants' claims as lacking a requirement that extracellular matrix production is enhanced without increasing cellular proliferation. For example, on page 12, the Examiner has stated:

> It is noted that none of the rejected claims recite the claimed method *enhances* extracellular matrix production without

> increasing cellular proliferation. Further, the claimed method does not require *inhibition* of cellular proliferation.

See ANSWER, at 12, ll. 16-19 (emphasis in original). Similar statements are made elsewhere in the Answer. For example, on page 13, the Examiner states:

> It is noted that claim 1 does not recite coupling a matrix-enhancing molecule to a tissue engineering scaffold in an effective density to *increase* extracellular matrix production without increasing cellular proliferation.

See id. at 13, ll. 17-20 (emphasis in original). Appellants respectfully disagree. Claim 1 clearly states:

> A method for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells bound to the scaffold comprising coupling matrix-enhancing molecules to the scaffold in an effective density to *elicit production of extracellular matrix without increasing cellular proliferation*. . . .

See, e.g., APPEAL BRIEF, Appendix: Claims As Pending, at 1. The word "elicit" is defined by the Oxford English Dictionary (2d. edition, 1989) as a transitive verb meaning, *e.g.*, "to draw forth (what is latent or potential) into sensible existence." *See id.* By "eliciting" production of extracellular matrix from cells bound to a tissue engineering scaffold, as recited in claim 1, Appellants' invention draws forth extracellular matrix into existence. This necessarily includes, *inter alia*, embodiments wherein extracellular matrix production *increases* from zero to a desired level. Therefore, contrary to the Examiner's suggestion, claim 1 clearly recites a method for making a tissue engineering scaffold wherein extracellular matrix production is enhanced, or increased, without increasing cellular proliferation.

When an Examiner asserts that a combination of references obviate a claim under 35 U.S.C. 103, the combination "must teach or suggest all the claim limitations." MPEP §2143, at 2100-124. The requirement that extracellular matrix production be elicited without increasing cellular proliferation is a limitation of claim 1 that must be met by the cited art in order to

obviate the claim under 35 U.S.C. 103. Here, however, the cited art fails to meet this limitation. As shown in Appellants' Appeal Brief, neither the Dinbergs *et al.* reference nor the WO 94/23740 reference discloses, or even suggests, the claimed method of coupling a matrix-enhancing molecule to a tissue engineering scaffold in an effective density to increase extracellular matrix production without increasing cellular proliferation. *See* APPEAL BRIEF, at 6-7 (discussing WO 94/23740); at 8-9 (discussing Dinbergs *et al*). Appellants respectfully assert that by improperly construing the scope of claim 1 as shown above, the Examiner has improperly rejected claim 1 as obvious in view of art that clearly does not meet, or suggest, each limitation in the claim.

2. WO 94/23740 fails to disclose several limitations of Appellants' claim 1.

Appellants' Appeal Brief demonstrates that WO 94/23740 fails to disclose several limitations of Appellants' claim 1. *See* APPEAL BRIEF, at 6-7.

a. WO 94/23740 fails to disclose a method of making a tissue engineering scaffold, or that matrix enhancing molecules may be coupled to the tissue engineering scaffold.

WO 94/23740 fails to disclose a method of making a tissue engineering scaffold, or that matrix enhancing molecules may be coupled to such a tissue engineering scaffold. The Examiner contends, in response, that WO 94/23740 teaches methods of making a tissue engineering scaffold. On page 8 of the Examiner's Answer, the Examiner states:

> The WO 94/23740 publication teaches a method for making a tissue engineering scaffold such as bone formation (See page 7, line 9-13, in particular) comprising coupling various matrix-enhancing molecules such as TGF-β or TGF-β2 to a polymer matrix such as polyethylene glycol. . . .

See ANSWER, at 8. Appellants respectfully assert that the Examiner has misinterpreted the WO 94/23740 disclosure. First, "bone formation" is not a "scaffold," it is simply the process by

which bone is formed. Indeed, nowhere in the WO 94/23740 publication is the word "scaffold" even mentioned. Rather, as stated in Appellants' Appeal Brief, "WO 94/23740 discloses a method for stimulating bone formation in an animal by administering to the animal an effective amount of a hydrophilic polymer-conjugated growth factor *in solution*." *See* APPEAL BRIEF, at 6 (emphasis added).

On page 8 of the Examiner's Answer, the Examiner further states:

> The WO 94/23740 publication further teaches that the reference matrix-enhancing molecule TGF-β is covalently coupled to tether or linking group such as hydroxysuccinimide to the scaffold such as the hydrophilic polymer such as polyethylene glycol . . . .

See ANSWER, at 8. Appellants respectfully assert that this, too, is a misapplication of the WO 94/23740 publication. As taught in WO 94/23740, the polymer (*e.g.*, the polyethylene glycol) is not a scaffold. Rather, the polymer is a substance that is conjugated with the growth factor, whereupon the polymer-conjugated growth factor is administered to an animal *in solution*. As taught in WO 94/23740, the polymers disclosed in WO 94/23740 are not themselves scaffolds, nor does WO 94/23740 even disclose tethering its polymer-conjugated growth factors to a scaffold. As taught in WO 94/23740, the polymers disclosed in WO 94/23740 are *systemically administered*, whereas the scaffolds of the present invention are *locally administered*. Accordingly, Appellants respectfully assert that WO 94/23740 does not disclose methods of making a tissue engineering scaffold, much less methods of making a tissue engineering scaffold involving coupling a matrix enhancing molecule to the scaffold, a limitation that is recited in Appellants' claim 1.

b. WO 94/23740 fails to disclose tethering a matrix enhancing molecule to a scaffold to increase extracellular matrix production without increasing cellular proliferation.

Appellants' Appeal Brief demonstrates that WO 94/23740 fails to disclose tethering a matrix enhancing molecule to a scaffold to increase extracellular matrix production without increasing cellular proliferation. *See* APPEAL BRIEF, at 7.

In response, the Examiner repeats her position that the "WO 94/23740 publication teaches a method for making a tissue engineering scaffold such as bone formation," and that the "WO 94/23740 publication further teaches that the reference matrix-enhancing molecule TGF-β is covalently coupled to tether or linking group such as hydroxysuccinimide to the scaffold such as the hydrophilic polymer such as polyethylene glycol. . . ." *See* ANSWER, at 9. Appellants have demonstrated above that the Examiner has misapplied the WO 94/23740 publication.

The Examiner further responds by stating, with reference to the WO 94/23740 publication:

> The claimed invention in claim 1 differs from the teachings of the reference only that the method for making a tissue engineering scaffold without increasing cellular proliferation and the TGF-β is in a density between 1 and 100 ng/ml. . .

See ANSWER, at 9. From this statement, it is apparent that the Examiner perceives the WO 94/23740 publication as disclosing everything in Appellants' claim 1, except for a different density of TGF-β for those embodiments of claim 1 wherein the matrix-enhancing molecule is TGF-β. Appellants respectfully submit that the Examiner greatly misperceives both the scope of Appellants' claim 1, and the content of the WO 94/23740 disclosure. As shown above, and in Appellants' Appeal Brief, the WO 94/23740 publication does not even disclose a method for making a tissue engineering scaffold, much less one that only differs from Appellants' claimed invention by the concentration of TGF-β and the failure to teach the inhibition of cellular

proliferation. Indeed, the WO 94/23740 publication merely discloses the use of hydrophilic polymer-conjugated growth factor *in solution*, not tethered to a scaffold.

The Examiner then attempts to rely on the Dinbergs *et al* publication to respond to Appellants' contention that WO 94/23740 fails to disclose tethering a matrix enhancing molecule to a scaffold to increase extracellular matrix production without increasing cellular proliferation (Appellants will discuss the shortcomings of the Dinbergs reference shortly). Accordingly, Appellants respectfully assert that the Examiner has failed to show that the WO 94/23740 publication discloses tethering a matrix enhancing molecule to a scaffold to increase extracellular matrix production without increasing cellular proliferation, as recited in Appellants' claim 1.

c. WO 94/23740 fails to disclose the tethering of TGF-β to a scaffold in an effective density of between 1-100 ng TGF-β/mL.

Appellants' Appeal Brief demonstrates that WO 94/23740 fails to disclose methods of tethering a matrix enhancing molecule to a scaffold to increase extracellular matrix production without increasing cellular proliferation, wherein when the matrix enhancing molecule is TGF-β, the TGF-β is used in an effective density of between 1-100 ng TGF-β/mL. *See* APPEAL BRIEF, at 7. The Examiner responds only by stating "The WO 94/23740 publication teaches that the method results affect variable which have been discussed supra," and then discusses the Dinbergs *et al* reference. *See* ANSWER, at 10. Accordingly, Appellants respectfully assert that the Examiner has failed to show that the WO 94/23740 publication discloses that, when TGF-β is used as a matrix enhancing molecule tethered to a tissue engineering scaffold, the TGF-β is present in an effective density of between 1-100 ng TGF-β/mL, as recited in Appellants' claim 1.

3. Dinbergs *et al* fails to disclose several limitations of Appellants' claim 1.

Appellants' Appeal Brief demonstrates that the Dinbergs *et al* reference fails to disclose several limitations of Appellants' claim 1. *See* APPEAL BRIEF, at 8-9.

a. Dinbergs *et al* fails to disclose a method of making a tissue engineering scaffold, or that matrix enhancing molecules may be coupled to the tissue engineering scaffold.

Dinbergs *et al* fails to disclose a method of making a tissue engineering scaffold, or that matrix enhancing molecules may be coupled to such a tissue engineering scaffold. On page 9 of the Examiner's Answer, the Examiner contends:

> Dinbergs *et al* teach a method for making a tissue engineering scaffold or formation of extracellular matrix by cells such as endothelial cells or smooth muscle cells seeded to the scaffold *such as plastic of a 12-well tissue cultured plate.* The reference method comprises coupling various matrix-enhancing molecule such as bFGF or TGFβ to a polymer such as alginate Heparin Sepharose microphere. . . .

See ANSWER, at 9 (emphasis added).

i. A 12-well tissue cultured plate is not a "scaffold."

Appellants respectfully assert that a 12-well tissue cultured plate cannot constitute a tissue engineering scaffold within the meaning of Appellants' claimed invention, and the disclosure in Dinbergs *et al* of seeding endothelial cells or smooth muscle cells to a 12-well tissue cultured plate does not teach a method for making a tissue engineering scaffold. The present invention contemplates implantation of the scaffolds within the body of a mammal where tissue is desired. *See, e.g.*, APPLICATION, at 8, lines 12-13 ("The scaffold is typically seeded with the cells; the cells are cultured, and then the scaffold implanted."). A 12-well tissue cultured plate, such as that used in the experiments conducted by Dinbergs *et al.*, would never be implanted within the body of a subject, for any reason. A 12-well tissue cultured plate is not an implantable article, rather, it is used *in vitro*.

ii. A microsphere is not a "scaffold."

Appellants respectfully assert that a microsphere, such as those used in Dinbergs *et al* to encapsulate TGFβ, is not a scaffold. The scaffolds of the present invention are "useful in not

only tissue engineering but also for tissue regeneration and wound healing applications." *See* APPLICATION, at 3, lines 3-5. In contrast, a single microsphere, being a discrete object having a microscopic size, could not by itself be thought capable of having any use in such applications. A scaffold of the present invention may be surgically implanted in the body of a mammal. *See, e.g.*, APPLICATION, at 8, lines 12-13 ("The scaffold is typically seeded with the cells; the cells are cultured, and then the scaffold implanted."). A single microsphere would not, *by itself*, be surgically implanted in the body of a mammal, quite unlike the scaffolds of the present invention, which are designed to be implanted into the body of a mammal.

iii. Conclusion

The growth factors in Dinbergs *et al* are not coupled to a polymeric scaffold, but instead are encapsulated by a polymeric matrix and released as soluble growth factors. Appellants respectfully assert that the Examiner has not shown that Dinbergs *et al* disclose a method of making a tissue engineering scaffold, or that matrix enhancing molecules may be coupled to such a tissue engineering scaffold, as contemplated by Appellants' claim 1.

b. Dinbergs *et al* fails to disclose tethering a matrix enhancing molecule to a scaffold to increase extracellular matrix production without increasing cellular proliferation.

Appellants' Appeal Brief demonstrates that WO 94/23740 fails to disclose tethering a matrix enhancing molecule to a scaffold to increase extracellular matrix production without increasing cellular proliferation. *See* APPEAL BRIEF, at 8-9.

In response, the Examiner repeats her position that Appellants' claims lack a requirement that extracellular matrix production is enhanced without increasing cellular proliferation. *See* ANSWER, at 12; *id.* at 13. Appellants have previously demonstrated herein, however, that the Examiner has erroneously perceived the scope of Appellants' claims, including claim 1.

The Examiner goes on to assert, at the bottom of page 12 of the Answer, that Dinbergs does disclose that the use of TGF-β coupled to alginate Heparin Sepharose microspheres does not increase cellular proliferation. *See* ANSWER, at 12. This portion of the Answer does not address the additional limitation of Appellants' claim 1, that extracellular matrix production must be enhanced without increasing cellular proliferation, but the Examiner does address this limitation elsewhere in the Answer, such as at pages 9-10, where the Examiner states:

> Dinbergs *et al*, teach TGFβ is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular).

The Examiner repeats this assertion, with minor variations, in numerous places throughout the Answer. Appellants respectfully would point out that Figures 3A and 3B of Dinbergs *et al.* make no mention of eliciting extracellular matrix formation at all. Furthermore, the TGFβ used in Figures 3A and 3B of Dinbergs *et al.* was "solvent-cast within EVAc microspheres," rather than tethered to a scaffold. *See* Dinbergs *et al* at 29824, 5th full paragraph. The growth factors in Dinbergs *et al* are not coupled to a polymeric scaffold, but instead are encapsulated by a polymer and released as soluble growth factors, quite unlike Appellants' invention.

The Examiner continues, on page 10 of the Answer:

> In fact, the *without* increasing cellular proliferation or cell number in smooth muscle cell as taught by Dinbergs *et al* is the same effect on the same cell type using the same TGFβ as disclosed on page 14, line 18-19 of instant specification.

See ANSWER, at 10 (emphasis in original). Appellants first would point out that, with reference to smooth muscle cells, Dinbergs *et al* actually demonstrate cell *proliferation*. This is clearly seen from Figure 3B of Dinbergs *et al*, where the cell number may be seen to have increased after even but a single day. By the second day of the experiment, about an additional 25,000

cells have proliferated. *See* Dinbergs *et al*, Figures 3B. Accordingly, Appellants respectfully assert that Dinbergs *et al* do not teach that administration of TGFβ may enhance extracellular matrix production without increasing proliferation in the number of smooth muscle cells. For the same reason, Appellants respectfully assert that the Examiner's statement that Dinbergs *et al* teach "the same effect" as disclosed in Appellants' specification is incorrect.

c. Dinbergs *et al* fails to disclose the tethering of TGF-β to a scaffold in an effective density of between 1-100 ng TGF-β/mL.

Appellants' Appeal Brief demonstrates that Dinbergs *et al* fails to disclose methods of tethering a matrix enhancing molecule to a scaffold to increase extracellular matrix production without increasing cellular proliferation, wherein when the matrix enhancing molecule is TGF-β, the TGF-β is used in an effective density of between 1-100 ng TGF-β/mL. *See* APPEAL BRIEF, at 9, lines 1-10. The Examiner responds by stating that Dinbergs does teach the use of TGF-β in the disclosed range, on the grounds that Dinbergs teaches a concentration of 3 ng TGF-β per microsphere, and that 5-10 microspheres are placed in 1 mL of PBS solution, thus equating to 15-30 ng TGF-β/mL of PBS. *See* ANSWER, at 13, ll. 6-12. Appellants respectfully reiterate that this is not a disclosure of the tethering of TGF-β to a tissue engineering scaffold in an effective density of between 1-100 ng TGF-β/mL of scaffold.

4. The combination of the WO 94/23740 and Dinbergs *et al* references fails to obviate claim 1.

Appellants have demonstrated that the combination of WO 94/23740 and Dinbergs *et al* references fails to obviate Appellants' claimed invention. *See* APPEAL BRIEF, at 10-11. For example, the combination fails to obviate claim 1. Neither reference discloses the coupling of matrix-enhancing molecules to a tissue engineering *scaffold*, and neither discloses coupling TGF-β to a scaffold in an effective density to enhance extracellular matrix production without increasing cellular proliferation. *See id.* In response, the Examiner states:

> The polymer-growth factor conjugate such as TGF-β coupled to the polyethylene glycol taught by the WO 94/23740 is identical to the polymer-growth factor conjugate as disclosed on page 9 line 24-25 of the specification.

See ANSWER, at 16. The Examiner's reference is to an Example in the present specification wherein conjugates of TGF-β with polyethylene glycol were prepared. This same Example further discloses, on page 11 of the present specification, lines 8-22, and particularly lines 13-20, that certain of the PEG-TGF-β conjugates then were tethered to a scaffold (*e.g.*, a hydrogel). Subsequent portions of the same Example disclose the unexpected results that occurred when the hydrogels comprising PEG-tethered TGF-β were seeded with smooth muscle cells. *See, e.g.*, APPLICATION, at 13 ("[T]he tethered peptides of TGF-β are covalently bound to the hydrogel structure via a highly flexible PEG chain"); and at 13-14 ("[S]ignificantly more hydroxyproline was produced when TGF-β was tethered onto the hydrogels than when soluble TGF-β was used").

Accordingly, the Examiner's assertion that the WO 94/23740 publication discloses conjugates of TGF-β with polyethylene glycol ignores the fact that the conjugates of the WO 94/23740 publication are administered to an animal in solution, whereas Applicants teach that unexpectedly superior results are achieved by, *e.g.*, tethering such conjugates to a scaffold (*e.g.*, a hydrogel).

Furthermore, the Examiner goes on to assert that:

> Dinbergs *et al.* teach that it is known at the time the invention was made that TGFβ has been incorporated into scaffold such as biodegradable polymer matrix made of collagen, hydrogels such as alginate, hydron (hyaluronic acid) and polyethylene glycol polymers (See page 29827, column 2, first full paragraph . . .).

See ANSWER, at 16. Appellants respectfully suggest that when the cited portion of Dinbergs *et al* is re-examined in context, the Examiner's application of Dinbergs *et al* may be seen to be in error. In context, the cited portion of Dinbergs actually states:

> Various polymeric devices have been used for the controlled release of a number of growth factors. . . . TGF-β1 has been delivered for the purpose of bone repair via the biodegradable polymer poly-(DL-lactide-co-glycolide) and demineralized bone matrix (69, 71, 70, 73), although problems of immunocompatibility, osteoinductivity, and osteoconductivity exist. Other polymer materials have included . . . polyethylene glycol (88), collagen (63, 77, 89) . . . Hydron (78, 83, 91) and other hydrogels, *but these all have various limitations such as shorter or suboptimal release times and difficulty of handling*. Microspheres consisting of the biocompatible and biodegradable polymer alginate have also been utilized for controlled release delivery of some growth factors. . . . TGF-β1 release from sodium alginate microspheres has been demonstrated as a potential *oral* gastrointestinal drug delivery system, *in which TGF-β1 is completely and rapidly released within 2 h after a low pH environment is changed to pH 7.4 (80)*. Our data now support the notion that in considering the burgeoning technology of controlled release, the different interactions these growth factors have with the extracellular matrix must be taken into account. *Sustained release should be reserved for those growth factors that are naturally sustain-released.*

Dinbergs *et al.*, at 29827, Col. 2, first full paragraph (emphasis added). In contrast to the Examiner's application of this portion of Dinbergs *et al.*, the text, in context, actually shows that:

- the prior art did disclose the use of collagen, polyethylene glycol polymers, hydron, and other hydrogels to deliver growth factors, but each one of these materials was found to be problematic, *e.g.*, demonstrating "shorter or suboptimal release times and difficulty in handling." *See id.*

- none of these disclosures cited in Dinbergs *et al*, nor even Dinbergs *et al* itself, disclosed tethering a growth factor to a scaffold. Nowhere in the above excerpt is either "tethering" or a "scaffold" mentioned. *See id.*

- the embodiment cited by the Examiner involving the use of alginate to release TGFβ actually appears to disclose some form of *oral medication*, rather than a scaffold. *See id.* (reporting "TGF-β1 release from sodium alginate microspheres has been demonstrated as a potential *oral* gastrointestinal drug delivery system."). As will be apparent from the discussion of scaffolds in the

Application, and herein, a "scaffold" would never be orally administered to a patient.

- the embodiment cited by the Examiner involving the use of alginate to release TGFβ actually discloses the "complete" and "rapid" release of TGFβ during a 2 hour period.

- the excerpt explicitly teaches away from the sustained release of growth factors, which constitutes a teaching away from Appellants' invention.

Accordingly, the excerpt from Dinbergs *et al*, when combined with WO 94/23740, fails to obviate Appellants' claim 1.

The Examiner further asserts that "none of the rejected claims recite coupling TGF-β in an effective density to *enhance extracellular matrix production* without increasing cell proliferation." *See* ANSWER, at 16. However, as Appellants have previously shown herein, the Examiner has erroneously construed the scope of Appellants' claims, including claim 1, by omitting consideration of all the limitations present therein.

Accordingly, Appellants have shown that the cited combination of Dinbergs *et al* with WO 94/23740 does not obviate claim 1. Furthermore, as claim 1 is nonobvious over the prior art, dependent claims 2-9 are similarly nonobvious.

B. The cited combination of Dinbergs *et al* with WO 94/23740 fails to obviate the additional limitations found in Appellants' dependent claims 2-9.

Appellants have demonstrated that the combination of WO 94/23740 and Dinbergs *et al* references is not only improper, but moreover, it fails to obviate additional limitations present in several of Appellants' dependent claims. *See* APPEAL BRIEF, at 10-11.

The Examiner's Answer notes that the Examiner has withdrawn her rejection of claim 2 that was previously asserted with respect to the cited combination of WO 94/23740 and Dinbergs *et al*. *See* ANSWER, at 2.

With respect to claims 3 and 5, Appellants note that neither of the cited references discloses coupling of matrix-enhancing molecules such as angiotensin II (claim 3) and ascorbic acid (claim 5) to a polymeric scaffold. With respect to claim 4, Appellants note that neither of the cited references discloses coupling matrix-enhancing molecules such as insulin-like growth factors to a polymeric scaffold. The Examiner has not controverted Appellants' assertion, and reiterates that she considers claims 3, 4, and 5 to be withdrawn from consideration. *See* ANSWER, at 16-17 (failing to compare the cited combination to the additional limitations present in claims 3 and 5). Appellants previously have traversed the Examiner's decision to remove these claims from consideration in the present case, *see* PETITION FOR RECONSIDERATION OF RESTRICTION REQUIREMENT, and continue to assert that these claims should be examined in conjunction with the present case. Accordingly, Appellants respectfully assert that the Examiner has failed to show that the cited combination obviates the additional limitations found in Appellants' claims 3, 4, and 5.

With respect to claim 6, Appellants note that neither reference discloses coupling matrix-enhancing molecules to tethers that are coupled to the scaffold. In response, the Examiner states "[t]he WO 94/23740 publication teaches matrix-enhancing molecules such as TGF-β are covalently coupled either directly or indirectly to tethers or linking group such as hydroxysuccinimide to the scaffold/matrix such as the hydrophilic polymer such as polyethylene glycol." *See* ANSWER, at 17 (citing page 11, ll. 10-28 of the WO 94/23740 publication in particular). As Appellants have previously demonstrated herein, however, the Examiner has misinterpreted the WO 94/23740 disclosure. As taught in WO 94/23740, the polymer (*e.g.*, the polyethylene glycol) is not a scaffold. Rather, the polymer is a substance that is conjugated with the growth factor, whereupon the polymer-conjugated growth factor is administered to an animal

in solution. As taught in WO 94/23740, the polymers disclosed therein are not themselves scaffolds, nor does WO 94/23740 even disclose tethering its polymer-conjugated growth factors to a scaffold. Accordingly, Appellants respectfully assert that the Examiner has failed to show that the cited combination obviates the additional limitation found in Appellants' claim 6.

With respect to claims 7 and 8, Appellants note that neither reference teaches the additional limitations of the scaffold being a hydrogel (claim 7), nor the hydrogel being formed of a polymer selected from the group consisting of alginate, collagen, hyaluronic acid, and polyethylene glycol polymers (claim 8). In response, the Examiner reiterates her position that "Dinbergs *et al* teach that it is known at the time the invention was made that TGFβ has been incorporated into scaffold such as biodegradable polymer matrix made of collagen, hydrogels such as alginate, hydron (hyaluronic acid) and polyethylene glycol polymers." *See* ANSWER, at 17 (citing Dinbergs *et al* at 29827, col. 2, first full paragraph in particular). However, as Appellants have previously demonstrated herein, an examination of the cited portion of Dinbergs *et al*, in context, reveals no disclosure of tethering TGFβ to a scaffold. Nowhere in the cited portion is either "tethering" or a "scaffold" mentioned. *See id.* Furthermore, the embodiment that the Examiner cites as disclosing "hydrogels such as alginate" actually discloses a form of oral medication, rather than a scaffold. Accordingly, Appellants respectfully assert that the Examiner has failed to show that the cited combination obviates the additional limitations found in Appellants' claims 7 and 8.

With respect to claim 9, Appellants note that neither reference teaches the matrix-enhancing molecules being TGF-β coupled to the hydrogel in a concentration of between about $4x10^{-6}$ and $4x10^{-3}$ nmol/mL. In response, the Examiner states "[c]laim 9 is included in this rejection because $4x10^{-6}$ and $4x10^{-3}$ nmol/ml is equivalent to between 5 and 100 ng/ml and

Dinbergs *et al* teach TGFβ at 15-30 ng/ml is effective for inducing formation of extracellular matrix by endothelial cell or smooth muscle cell without increasing cell proliferation." *See* ANSWER, at 5. However, as Appellants have previously demonstrated herein, Dinbergs *et al* do not teach that TGFβ may be tethered to a scaffold, such as a hydrogel, to induce formation of extracellular matrix without increasing cell proliferation. Dinbergs *et al* fail to teach that TGFβ may be tethered to a scaffold, and, particularly with respect to smooth muscle cell, fail to teach that extracellular matrix may be increased without increasing cell proliferation. Accordingly, Appellants respectfully assert that the Examiner has failed to show that the cited combination obviates the additional limitation found in Appellants' claim 9.

II. The combination of Dinbergs *et al.* and WO 96/27657 fails to obviate Appellants' claimed invention.

A. The Examiner's rejection of claim 1 under 35 U.S.C. 103 in view of the combination of Dinbergs *et al.* and WO 96/27657 is improper.

Appellants' Appeal Brief demonstrated that Claim 1 is novel and nonobvious over the cited combination of WO 96/27657 and Dinbergs *et al*. *See* APPEAL BRIEF, at 11-13. Appellants respectfully assert that the Examiner's Answer fails to rebut Appellants' contention that claim 1 is novel and nonobvious over the cited references, for at least the following reasons.

1. WO 96/27657 teaches away from the present invention.

Appellants' Appeal Brief demonstrates that WO 96/27657 teaches away from the claimed invention. *See* APPEAL BRIEF, at 11-12. In response, the Examiner disagrees, and states that the cell growth taught by WO 96/27657 is not cell proliferation, but rather, "the definition of cell growth as taught by the WO 96/27657 is to enhance the long term stability of differentiated mammalian cells, or to enhance the biological response of the cell." *See* ANSWER, at 18 (citing WO 96/27657, at 1, ll. 12-19, and at 4). Appellants respectfully disagree. Nowhere in the excerpts referenced by the Examiner, or anywhere else in WO 96/27657, is cell growth explicitly

defined in any way. Rather, the excerpts cited by the Examiner simply state desirable attributes of nonspecific "methods and materials." Furthermore, the same Background section cited by the Examiner also notes, "[u]sing current methodology, it is difficult to grow normal liver cells *in vitro* beyond two to three cell divisions," (*see* WO 96/27657, at 1, ll. 24-25)—a reference to cell proliferation. The Background further discusses studies that have been conducted "to improve the viability, *proliferation* and differentiated function of eukaryotic cells . . .," and links this to "cell growth" by emphasizing a discovery made by one of these studies that facilitated cell growth. *See* WO 96/27657, at 2, ll. 3-7.

It is unquestioned that cell growth is an important part of the WO 96/27567 disclosure—indeed, it is expressly stated to be an object of the invention disclosed therein. *See id.* at 3, ll. 21-27. No support can be found in WO 96/27657 for the Examiner's limitation of the term "cell growth" to exclude cell proliferation. Rather, the methods that facilitate cell growth that are disclosed in WO 96/27657 are properly understood to promote cellular proliferation, which teaches away from Appellants' claimed invention.

2. WO 96/27657 does not disclose a method of enhancing production of extracellular matrix molecules.

Appellants have demonstrated that WO 96/27657 does not disclose a method of enhancing production of extracellular matrix molecules. *See* APPEAL BRIEF, at 11-12. The Examiner responds by asserting that WO 96/27657 discloses "tissue regeneration such as production of extracellular matrix proteins such as collagen." *See* ANSWER, at 19 (citing WO 96/27657 at 17, ll. 1-4). Appellants respectfully reassert a point made in Appellants' Appeal Brief, which the Examiner has failed to controvert—the referenced text from WO 96/27657 is directed to materials for construction of tissue regeneration devices, and lists collagen as a candidate material because it is a natural polymer. This is not at all a disclosure of the

production of an extracellular matrix protein. Accordingly, Appellants respectfully assert that the Examiner has failed to demonstrate any disclosure in WO 96/27657 of a method of enhancing production of extracellular matrix molecules, as recited in Appellants' claim 1.

3. WO 96/27657 does not disclose, in the case of TGF-β, an effective density of 1-100 ng TGF-β/ml.

Appellants have demonstrated that WO 96/27657 does not disclose, in the case of TGF-β, an effective density of 1-100 ng TGF-β/ml. *See* APPEAL BRIEF, at 11-12. The Examiner agrees with this assertion. *See* ANSWER, at 19.

4. There is no suggestion in either WO 96/27657 or Dinbergs *et al* to incorporate the teachings of the other.

Appellants have demonstrated the utter absence of a suggestion in either WO 96/27657 or Dinbergs *et al* to incorporate the teachings of the other. *See* APPEAL BRIEF, at 12. Therein, Appellants highlighted the teachings in Dinbergs that TGF-β weakly inhibits cellular proliferation, which contrasts with the intent of WO 96/27657, which is to promote cellular proliferation. Because one reference teaches the inhibition of cell growth, while the other reference teaches the promotion of cell growth, the references cannot be combined. For that reason and other reasons asserted in Appellants' Appeal Brief, at 12, the Dinbergs reference and the WO 96/27657 reference are incompatible and cannot be combined. In response, the Examiner reiterates her position that WO 96/27657 is not directed to enhancing cellular proliferation—a position that Appellants respectfully assert is incorrect, as Appellants have demonstrated herein.

5. Even if the WO 96/27657 and Dinbergs *et al* references are combined, the combination fails to obviate claim 1.

Appellants have demonstrated that the combination of WO 96/27657 and Dinbergs *et al* references is not only improper, but moreover, it fails to obviate Appellants' claimed invention.

See Appeal Brief, at 12-13. For example, the combination fails to obviate claim 1. Neither reference discloses the benefit of enhancing extracellular matrix formation without increasing cellular proliferation, and neither discloses coupling TGF-β to a polymeric scaffold in an effective density between 1-100 ng/mL. In response, the Examiner reiterates her position that none of Appellants' claims are drawn to a method of enhancing extracellular matrix formation without increasing cellular proliferation (*see* ANSWER, at 21)—a position that Appellants respectfully assert is incorrect, as Appellants have demonstrated herein. The Examiner then goes on to assert a motivation to combine the cited references, but fails to demonstrate that the combined references discloses a method of enhancing extracellular matrix formation without increasing cellular proliferation, and fails to demonstrate that the combined references disclose coupling TGF-β to a polymeric scaffold in an effective density between 1-100 ng/mL. Accordingly, even if the cited references are combined, the Examiner has failed to show how the combination obviates claim 1. As claim 1 is nonobvious over the prior art, dependent claims 2-9 are similarly nonobvious.

B. Even if the WO 96/27657 and Dinbergs *et al* references are combined, the combination fails to obviate the additional limitations found in Appellants' dependent claims 3, 5, and 7-9.

Appellants have demonstrated that the combination of WO 96/27657 and Dinbergs *et al* references is not only improper, but moreover, it fails to obviate the additional limitations present in several of Appellants' dependent claims. *See* Appeal Brief, at 13.

With respect to claims 3 and 5, Appellants note that neither of the cited references discloses coupling of matrix-enhancing molecules such as angiotensin II (claim 3) and ascorbic acid (claim 5) to a polymeric scaffold. The Examiner does not controvert Appellants' assertion. *See* ANSWER, at 19-20 (failing to compare the cited combination to the additional limitations

present in claims 3 and 5). Accordingly, even if the cited WO 96/27657 and Dinbergs *et al* references are combined, Appellants respectfully assert that the Examiner has failed to show that the cited combination obviates the additional limitations found in Appellants' claims 3 and 5.

With respect to claims 7 and 8, Appellants note that neither reference teaches the additional limitations of the scaffold being a hydrogel (claim 7), the hydrogel being formed of a polymer selected from the group consisting of alginate, collagen, hyaluronic acid, and polyethylene glycol polymers (claim 8). In response, the Examiner reiterates her position as to the teachings of both the WO 96/27657 and Dinbergs *et al* references, but does not appear to clearly address claims 7-8, except to repeat her earlier position that "Dinbergs *et al* further teach that TGFβ has been incorporated into scaffold or various biodegradable polymer matrix such as collagen, hydrogels such as alginate . . . ." *See* ANSWER, at 20 (citing Dinbergs *et al.*, at 29827, Col. 2, first full paragraph). However, as Appellants have previously stated herein, the cited portion of Dinbergs *et al* is not helpful to the Examiner's argument, for at least the following reasons: (i) it teaches away from each of the cited materials, stating that each was found to be problematic and difficult to handle; (ii) it does not disclose the use of a scaffold; and (iii) the embodiment that the Examiner cites as disclosing "hydrogels such as alginate" actually discloses a form of oral medication, rather than a scaffold. Accordingly, even if the cited WO 96/27657 and Dinbergs *et al* references are combined, Appellants respectfully assert that the Examiner has failed to show that the cited combination obviates the additional limitations found in Appellants' claims 7 and 8.

With respect to claim 9, Appellants note that neither reference teaches the matrix-enhancing molecules being TGF-β coupled to the hydrogel in a concentration of between about $4x10^{-6}$ and $4x10^{-3}$ nmol/mL. In response, the Examiner states "between $4x10^{-6}$ to $4x10^{-3}$ nmol/ml

is equivalent to between 5 and 100 ng/ml and Dinbergs *et al* teach TGFβ at 15-30 ng/ml is effective for inducing formation of extracellular matrix by endothelial cell and smooth muscle cell without increasing cell proliferation." *See* ANSWER, at 20 (citing Figures 3A and 3B of Dinbergs *et al*). However, as Appellants have previously pointed out herein, Dinbergs *et al* actually demonstrate *an increase in cell proliferation*, with respect to smooth muscle cells that have been exposed to TGFβ. *See, e.g.*, Dinbergs *et al*, Figure 3B. Additionally, Figures 3A and 3B of Dinbergs *et al* make no mention of eliciting extracellular matrix formation at all. *See id.* Accordingly, even if the cited WO 96/27657 and Dinbergs *et al* references are combined, Appellants respectfully assert that the Examiner has failed to show that the cited combination obviates the additional limitation found in Appellants' claim 9.

III. Appellants have demonstrated that the claimed methods have produced unexpected results in view of the prior art.

Appellants' Appeal Brief demonstrates that the claimed methods have produced unexpected results in view of the prior art. *See* APPEAL BRIEF, at 13-15 (noting that Appellants' invention has resulted in an unexpectedly improved method of enhancing extracellular matrix formation without an increase in cell proliferation); *see also* APPLICATION, Tables 5 and 6 (demonstrating an increase in extracellular matrix formation without a corresponding increase in cellular proliferation). In response, the Examiner once again reiterates her position that Appellants' claims do not recite a method of *enhancing* extracellular matrix formation without an increase in cell proliferation. *See* ANSWER, at 24. However, as Appellants' have previously shown herein, the Examiner has erroneously construed the scope of Appellants' claims by omitting consideration of all the limitations present therein. Appellants' claims do recite a method of enhancing extracellular formation without an increase in cell proliferation, as Appellants have shown herein.

The Examiner repeats a number of arguments that have been previously addressed herein and have been shown to be misapplications of the prior art. For example, the Examiner states:

> In fact, the *without* increasing cellular proliferation or cell number in smooth muscle cell as taught by Dinbergs *et al* is the same effect on the same cell type using the same TGFβ as disclosed on page 14, line 18-19 of instant specification.

See ANSWER, at 26 (emphasis in original). Here again, the Examiner has incorrectly applied the prior art. With reference to smooth muscle cells, Dinbergs *et al* actually demonstrate cell *proliferation*. This is clearly seen from Figure 3B of Dinbergs *et al*, where the cell number may be seen to have increased after even but a single day. By the second day of the experiment, about an additional 25,000 cells have proliferated. *See* Dinbergs *et al*, Figures 3B. Accordingly, Appellants respectfully assert that Dinbergs *et al* do not teach that administration of TGFβ may enhance extracellular matrix production without increasing proliferation in the number of smooth muscle cells. For the same reason, Appellants respectfully assert that the Examiner's statement that Dinbergs *et al* teach "the same effect" as disclosed in Appellants' specification is incorrect.

For at least the reasons presented herein, Appellants respectfully assert that the Examiner has failed to disprove Appellants' statement that Appellants' claimed invention achieves unexpected results in view of the prior art, and is therefore nonobvious to one of ordinary skill in the art.

IV. Conclusion and requested relief.

Appellants respectfully state that they have demonstrated that claims 1-9 are novel and nonobvious over the prior art. Accordingly, Appellants request (i) that the rejection under 35 USC 103, in view of Dinbergs *et al* and WO 94/23740, be withdrawn, (ii) that the rejection under 35 USC 103, in view of Dinbergs *et al* and WO 96/27657, be withdrawn, and (iii) that the case be remanded to the Examiner for further consideration.

Respectfully submitted,

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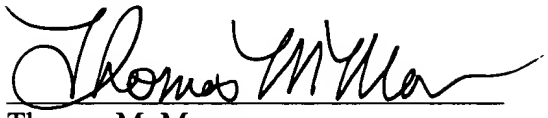

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